UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,699	01/25/2001	Saul J. Silverstein	61152-A/JPW/AJM/HA	5342

7590 02/25/2004

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,699	SILVERSTEIN ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/11/2003 has been entered.

In the response filed 8/11/2003, several claims were amended (claims 1, 5 & 9). Claims 1-7, 9 and 11 are pending and under consideration in this application. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9 & 11 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in Paper No. 14 mailed in April 8, 2003. A response to applicants' arguments follows.**

Response to Arguments/Written Description

Applicant's arguments filed 8/11/2003 have been fully considered but they are not persuasive. The response essentially argues: **1)** it is unnecessary for applicants to set forth the sequence(s) of naturally occurring protein variants for the written description requirement to be satisfied, **2)** SEQ ID NO: 2 provides a sufficiently representative embodiment to describe the broadly claimed genus for the purposes of written description, **3)** identifying naturally-occurring variants of SEQ ID NO: 2 would not require undue experimentation, **4)** applicants have shown that 29p will enter mammalian cells and methods exist in the art for affixing agents to a protein without eliminating the protein's functional properties, **5)** applicants need not teach the specific 29p domains responsible for cell entry for this purpose, **6)** the term "agent" is clearly defined throughout the specification (e.g. page 9, lines 22-33; page 10, lines 1-24), **7)** the specification need not contain an example of the invention if the invention is otherwise disclosed in such a manner that the skilled artisan would be able to practice it without undue experimentation, **8)** the Berendsen reference is inapplicable because it does not specifically mention the 29p protein, and **9)** the 29p protein need not have an affinity for or naturally bind to the agent (i.e. in response to the statement made by the examiner that "the 29p protein must retain the ability to bind to any agent").

The response filed 8/11/2003 essentially restates each of the arguments made previously in response to these grounds of rejection. For this reason, all of the counter arguments made by the examiner in the Final office action mailed as Paper No. 14 are incorporated here by reference.

To summarize those counter arguments, applicants are claiming a composition of matter comprising a combination of 29p protein/agent covalently attached thereto/host cell type where the 29p protein retains the structural characteristics to allow it to mediate entry of the agent into the target host cell. The assertion that the 29p protein by itself provides sufficient description of the structural characteristics of the protein to allow one to envision a sufficient number of embodiments to describe the broadly claimed genus of combinations of 29p protein/agent covalently attached thereto/host cell type where the 29p protein retains the structural characteristics to allow it to mediate entry of the agent into the target host cell is unsupported by description or example in the prior art or specification. Applicants have not described a *single example* where *any* variant of the 29p protein has an agent of *any* type covalently attached to it and where the 29p protein mediates entry of the agent into *any* cell type. Nowhere in the prior art or instant specification is there a description of the domains within native 29p protein that allow it to bind to and enter cells of any type. Such a characterization of the 29p protein might allow one to predictably envision at least one embodiment that would necessarily meet the functional limitations of the claims (i.e. a 29p variant comprising an agent covalently attached thereto where the combination meets the functional limitations of the claims). Nor is there a description of the type of receptor(s) responsible for allowing entry of the composition into the cell. Such a description conceivably might provide some information regarding the three-dimensional folding characteristics of the 29p protein that would allow one to envision modifications of the 29p protein (including covalent attachments) that would allow the modified protein to function.

With regard to methods of screening for specific combinations of 29p protein/agent covalently attached thereto/host cell type that meet the functional limitations of the claims, these arguments are of little or no weight in response to a rejection for lack of written description and are better suited to an enablement rejection. With regard to the Berendsen reference, this reference is applicable to the present rejection because it discusses the difficulty in the art for predicting the 3 dimensional structural/functional characteristics for *any* protein based on the primary sequence alone. Again, with regard to the functional domains within the 29p protein for entry into mammalian cells, the *only* information provided by the prior art and instant application is the primary amino acid sequence. Therefore, the reliability of any prediction as to how a particular variant or modified 29p will function in the context of the claim limitations is an issue with regard to sufficiently describing the claimed invention. As taught by Berendsen, such predictions based on primary sequence alone are *not* reliable. With regard to the ability of the 29p variant to "retain the ability to bind any agent", as explained in the argument section of the Final office action, the examiner was using the term "bind" in the broader sense of how the binding (including covalent linkage) affects the 3 dimensional folding of the 29p protein and its ability to mediate entry into mammalian cells. The examiner concedes there are and were techniques known in the art for forming covalent linkages between different compounds and proteins. The problem is in predicting the effect of such covalent linkage on the protein's structural/functional characteristics.

Claims 1-7, 9 & 11 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in Paper No. 14 mailed in April 8, 2003. A response to applicants' arguments follows.**

Response to Arguments/Enablement

Applicant's arguments filed 8/11/2003 have been fully considered but they are not persuasive. The response essentially argues: **1)** the traversal is based in part upon the arguments presented against rejection of the same claims for lack of written description, applicants disagree that the invention is complex, **2)** the breadth encompassed by the claims is relatively narrow, embracing only mammalian cells, **3)** the experiments in the specification showing 29p entry into mammalian cells, combined with routine methods of covalently affixing agents to proteins and identifying naturally occurring protein variants would enable the skilled artisan to practice the invention without undue experimentation, and **4)** the concept of using a protein that can readily enter a mammalian cell to deliver an agent to the cell was known in the art at the time of the invention.

To the extent that any of the examiner's arguments made above are applicable here, they are incorporated here by reference. Likewise, to the extent that any of the comments made in the Final office action by the examiner in response to applicants' arguments concerning enablement, those comments are incorporated here by reference. Again, applicants' arguments are essentially a restatement of the same arguments made previously.

With regard to the complexity of the invention, the invention is complex in that it relies upon the ability of a given protein to be delivered into the interior of any mammalian cell, even

in the context of a modified form of the protein wherein it is covalently attached to some undefined agent. The invention relies on the 3 dimensional structural/functional characteristics of a protein that can apparently bind some unidentified receptor(s) on the surface of some mammalian cells to deliver the protein and its cargo to the interior of the target cell. There is however, no significant guidance provided by the instant specification regarding what domains can be modified in the 29p protein by changes in amino acid sequence (i.e. "variants") and/or covalent linkage of an "agent" to the protein where the protein retains the ability to enter mammalian cells. Likewise, there is no guidance in the prior art or the specification as to the target receptor(s) on the surface of the target cells. Therefore, for at least these reasons, attempting to practice even one embodiment of the claimed invention would involve experimentation of an unpredictable, trial-and-error nature.

The assertion concerning the breadth encompassed by the rejected claims is accurate to a limited degree. It is true that a genus including only mammalian cells is narrower than a genus encompassing any cell. Yet, there are an incredibly large number of cell types that fall within the claimed genus of mammalian cells and within the genus including all mammalian cells, there are an undetermined number that may possess the ability for 29p to enter the cell. Since the process of how 29p functions to enter cells and the receptor(s) responsible for its translocation remain uncharacterized, the breadth of the genus of cells encompassed by the rejected claims greatly exacerbates the complexity of the invention.

To practice the claimed invention the skilled artisan would first have to envision a combination of 29p variant, target host cell, "agent" (e.g. small drug compound, peptide, nucleic acid, etc.), where and how to make a covalent linkage, means and dosage for delivery, etc. The

skilled artisan would then have to produce the 29p/agent composition and perform the experiments to determine the ability of the modified 29p protein to deliver the agent into the target cell. If unsuccessful, which is likely given the lack of significant guidance from the instant specification with regard to the functional domains of 29p and the identity of any receptor(s) involved in the translocation process, the skilled artisan would have to repeat the entire, unpredictable process until successful, if ever. Therefore, for these reasons and those outlined in making the rejection, it would have required undue, unpredictable experimentation of a trial-and-error nature to make and use the claimed invention. Such experimentation cannot be considered as to be routine in nature.

While it is true that the concept of using a protein to mediate delivery of an agent into the interior of a target cell was known in the art at the time of the invention, applicants' response does not teach the structural/functional characteristics shared by the prior art proteins and 29p that would make practicing the claimed invention any more predictable. Therefore, this argument is not persuasive.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9 & 11 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is maintained for reasons of record in Paper No. 14 mailed in April 8, 2003. A response to applicants' arguments follows.**

Response to Arguments/112 2nd Rejection

Applicant's arguments filed 8/11/2003 have been fully considered but they are not persuasive. The response essentially argues: **1)** naturally occurring variants of the 29p protein can be readily identified, **2)** the meaning of the term "naturally occurring variant" would be clearly understood by one skilled in the art, and **3)** so long as the metes and bounds of the claims are clear, it is irrelevant for the purposes of 112 2nd paragraph whether the specific sequences of such variants, or the various domains of the protein are actually set forth in the application.

Applicants' arguments are unconvincing in that there remains no basis for determining whether a particular variant of the 29p protein is "naturally-occurring" or not. The rejection was not made in terms of 112 1st paragraph (i.e. characterization of domains, etc.), but rather on the ability of the skilled artisan to know whether or not a particular variant of 29p, having the desired functional activity, constitutes a "naturally-occurring variant" of the protein. Is the skilled artisan required to determine if a particular cannot be found in anywhere in "nature"? Applicants' response does not address this issue.

Conclusion

No claims are allowed.

This is a continuing examination of applicant's earlier Application No. 09/769,699. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a

first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER